What's New in Melanoma

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KEYWORDS

• Melanoma epidemiology • Risk factors • Diagnosis • Prognosis • Management • Genomics

KEY POINTS

- The incidence of melanoma continues to increase, with a lifetime risk of 1 in 24 persons developing melanoma, but mortalities are decreasing because of increased awareness, early detection, and the availability of targeted therapies for advanced tumors.
- Primary prevention efforts to decrease the incidence of melanoma through behavior changes are less effective than secondary prevention efforts directed at early detection.
- Researchers continue to elucidate the myriad risk factors that predispose individuals to melanoma, including inflammatory bowel disease, phosphodiesterase-5 use, and pregnancy-diagnosed melanoma.
- Genomics and noninvasive devices are revolutionizing clinical management of melanoma, specifically through gene expression.
- Combination targeted therapies (double and triple pathway inhibition) are now being used to treat advanced melanoma.

INTRODUCTION

Issues related to melanoma are some of the most dynamic within dermatology (**Fig. 1**). Recent discoveries and new technologies have led to major advances in the diagnosis, management, and treatment of this cancer. As the incidence of melanoma continues to increase, understanding and applying these new approaches in the clinical setting has become increasingly important. From deciding whether to biopsy a suspicious pigmented lesion, to making an accurate diagnosis of an uncertain histopathologic presentation, to using genomics to better assess diagnosis and prognosis, to selectively targeting immune checkpoints that are dysregulated in melanoma, the management of melanoma has advanced greatly in the past few years. A comprehensive understanding of these issues is critical for dermatologists in the clinical setting.

EPIDEMIOLOGY

In the United States, there will be more than 90,000 cases of invasive melanoma and more than 87,000 cases of melanoma in situ diagnosed in 2018.[1] This incidence yields a lifetime risk of 1 in 24 persons for developing any type of melanoma. Among reported cancers, melanoma is the fifth most common in men and sixth most common in women.[2] Men are at a 40% increased risk to develop invasive melanoma in their lifetimes compared with women.[1]

Melanoma is one of the few cancers in the United States for which the incidence continues to increase. The lifetime risk of invasive melanoma in the United States has tripled from 1985 to 2018 and is projected to continue increasing.[1] Similarly, melanoma incidence has been increasing worldwide.[3]

Melanoma remains the deadliest form of skin cancer, accounting for 70% of skin cancer deaths.

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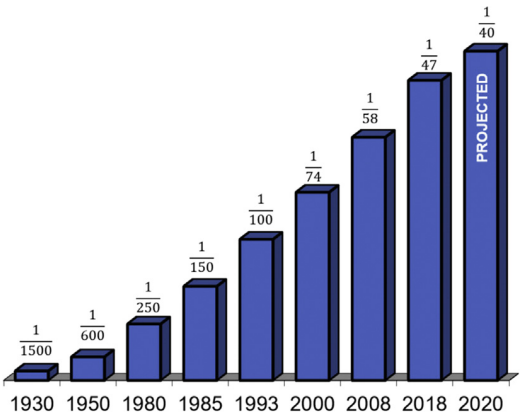

Fig. 1. Lifetime risk of invasive melanoma in the United States from 1930 to a projected risk in 2020.

More than 1 American dies from melanoma every hour. However, because of earlier detection and more effective treatments for melanoma, the absolute number of deaths in the United States has been decreasing since 2017 after peaking at about 10,000 in 2016.[4]

RISK FACTORS

Ultraviolet (UV) exposure and genetic predisposition (skin phenotype) remain the most important risk factors for the development of melanoma.[5–7] However, recent studies have shown other factors that may be contributory to melanoma risk.

Studies researching the effect of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs) on melanoma have had conflicting results.[8] Five studies showed a protective effect of aspirin and NSAID use on melanoma, whereas 4 studies showed no protective effect. Given the proven beneficial effects on cardiovascular health and colon cancer, daily aspirin or NSAID use may be beneficial for patients with an increased risk of melanoma, such as patients with dysplastic nevus syndrome or positive family history. A more recent study of 1522 patients with melanoma found that aspirin use was associated with longer overall survival in patients with stage 2 and 3 melanoma.[9] This finding warrants future clinical trials to investigate the therapeutic potential of aspirin in patients with melanoma.

Coffee has also been purported to be chemopreventive in melanoma. A meta-analysis of 7 studies found that higher coffee consumption was associated with a 0.8 times reduced risk of melanoma.[10] Decaffeinated coffee was not found to have the same effect. Another meta-analysis of 23 studies encompassing more than 2 million participants found the same effect: the persons with the highest levels of coffee consumption had a lower melanoma risk.[11] The investigators reported a dose-response relationship between coffee consumption and melanoma risk in which an increase in 1 cup of coffee per day resulted in a 3% decrease in melanoma risk.

Inflammatory bowel disease (IBD) has been associated with an increased risk of melanoma. In a recent meta-analysis of 12 studies comprising 172,837 patients with IBD, the investigators found a 37% increased risk of melanoma.[12] This rate was consistent among both Crohn disease and ulcerative colitis.

Phosphodiesterase-5 inhibitor use has been associated with an increased risk of developing melanoma. A meta-analysis of 5 observational studies found a slightly increased risk (odds ratio, 1.12).[13] However, there were no prospective studies available for analysis to confirm the association.

Women who are diagnosed with melanoma during pregnancy are at increased risk for recurrence. In a study of 462 women less than 49 years old with a history of melanoma, pregnancy-associated melanoma was associated with a 9 times increased risk of recurrence, a 7 times increased risk of metastasis, and a 5 times risk of mortality.[14] It is recommended that patients diagnosed with melanoma during pregnancy or within 1 year of childbirth be followed more closely.

The association between vitamin D level and melanoma has also been studied. A study of 1191 patients followed for 11 years found that a higher baseline vitamin D level was associated with a 2.7 times increased risk for melanoma.[15] The investigators concluded that the carcinogenicity of high sun exposure cannot be counteracted by higher vitamin D levels. Therefore, increasing vitamin D levels should be accomplished by dietary supplementation instead of through sun exposure.

PREVENTION

Primary prevention of skin cancer (behavioral changes) affects the incidence of melanoma, whereas secondary prevention (early detection efforts) affects the mortality. Based on the epidemiologic data presented earlier, secondary prevention seems to be making an impact through decreased mortality of melanoma, whereas primary prevention efforts have not led to a decreased number of cases at this point.

Behavioral change can lead to reduced risk for the development of this cancer. A primary prevention campaign directed at student athletes found

that, after an educational intervention, the participants were more likely to use sunscreen 4 or more times per week, recognize their increased risk of skin cancer, and participate in discussions about sun safety with coaches.[16]

Earlier detection initiatives can also lead to improved mortality. A secondary prevention effort that increased the early detection of melanoma among women undergoing mammography seemed to achieve its desired outcome.[17] Educational materials about skin self-examination were placed in changing rooms of mammography clinics. Most women noticed the materials on their own and were able to identify at least 1 personal risk factor for melanoma. After seeing the materials, 20% of the women performed a skin self-examination in the changing room and, of these, 13% noticed a concerning mole and most intended to follow up with a dermatologist.

As discussed earlier, patients with melanoma are more likely to develop further melanomas. Targeting these patients for preventive interventions is of high importance. A systematic review of behavioral intervention techniques for high-risk patients with melanoma found that most interventions resulted in increased photoprotective behaviors among participants, such as wearing protective clothing and engaging in skin self-examination.[18]

For these high-risk patients, the skin self-examination can mean the difference between life and death. However, it is difficult to examine the entire body surface area without a partner. Organizations such as the American Academy of Dermatology have advanced Check Your Partner campaigns to address this obstacle to skin self-examination.[19] A clinical trial of 494 patient-partner couples randomized to skin self-examination training or control showed that the training increased the frequency of examinations reported throughout the 2-year study period.[20]

Sunscreen

Regular sunscreen use decreases melanoma risk.[21,22] There has been long-standing debate over whether higher sun protection factor (SPF) sunscreens protect against UV radiation more than sunscreens with lower SPF. Opponents claims that increased SPF can lead to a false sense of security among users and increased time spent in the sun. Supporters argue that increased SPF makes up for the low concentrations of sunscreen applied by the average sunscreen user.

Controversy exists regarding the questions of whether there should there be a cap of 50+ on sunscreen SPFs (**Table 1**). Proponents suggest that higher SPFs cost disproportionately more, higher values seem to have disproportionally higher protection, and higher SPF sunscreens have higher concentrations of sunscreening agents that may lead to increased allergic reactions. Opponents cite the facts that people underapply sunscreens so higher SPFs are more forgiving at real-world application levels, that fair-skinned persons or those in high-insolation environments are not able to determine whether 50+ sunscreens are 51 or significantly higher, and that there will be no incentive to research and develop more protective sunscreens if manufacturers will not get credit. Almost half of the world currently has a 50+ cap, whereas the remaining countries do not.

In an attempt to help settle this issue, a double-blind randomized controlled trial of 199 patients showed that SPF 100+ is more effective at protecting against sunburn than SPF 50+ in real-world conditions in all skin types.[23] The results of the split-face study showed that the side randomized to SPF 50+ was 11 times more likely to be sunburned than the SPF 100+ side. The participants used the same amounts of sunscreen and reapplied equally on both sides. Even when analyzing for number of reapplications and

Table 1
Benefits and disadvantages of capping sunscreen sun protection factors at 50+

Benefits	Disadvantages
• Above SPF 50, doubling SPF values only results in a very small marginal additional protection	• Higher SPF sunscreens still can provide reasonable protection when underapplied at typically used concentrations
• Lower cost of sunscreens because higher SPF sunscreen is disproportionately more expensive	• No ability to discern between SPF 51 and higher SPFs for persons who may need greater protection
• Potentially fewer allergic reactions caused by lower concentrations of sunscreening agents	• No incentive for manufacturers to develop higher SPF sunscreens because no credit will be recognized
• More uniform reporting of SPF by manufacturers	• Decreased sun protection will be available to patients, potentially leading to increased skin cancer
• Less variability in claims about sunscreens	

Fitzpatrick skin type, higher SPF was still more protective.

Extensive controversy has recently unfolded over the inclusion of oxybenzone in sunscreen. Hawaii went as far as to ban the ingredient in sunscreens purchased in that state because of concerns about environmental toxicity to coral. Oxybenzone has been mired in controversy for a long time because of nonhuman studies that found estrogenic effects in the uteruses of rats. However, none of the evidence cited against oxybenzone has been found in humans or in conditions reflective of marine environments.[24] At present, the risk is entirely theoretic, but a ban on a key sunscreen ingredient will be sure to have long-lasting effects on skin cancer rates.

Complementary Sun Protection Supplements

Catechins, ingredients found in green tea, have been purported to decrease direct DNA damage induced by solar radiation. However, a double-blind randomized controlled trial in 50 patients receiving an oral green tea catechin extract with vitamin C or placebo did not find a significant difference in the number of cyclobutane pyrimidine dimer–positive cells in epidermis irradiated with UV.[25]

Polypodium leucotomos (PL) is a fern native to South America that is used for its antioxidant and photoprotective properties. The extract from this plant does not act as a sunscreen but has been shown to have some photoprotective efficacy. A recent systematic review of the clinical safety and efficacy of PL extract included 18 human studies to support its use as an additional sun-protective measure.[26] There were no reported serious adverse effects and the most commonly reported side effect was mild gastrointestinal discomfort.

Future prevention efforts should focus on preventing new melanomas through both primary and secondary prevention initiatives. To be effective there must be a comprehensive approach including UV protection (sunscreen, UV-blocking clothing, avoiding the midday sun), thereby minimizing the number of lifetime sunburns and initiatives that facilitate earlier detection through increased awareness and better access to dermatologic care.

DIAGNOSIS

Diagnostic Devices

Electrical impedance spectroscopy

The accuracy of clinical diagnosis in melanoma using the unaided human eye alone is about 70%.[27] Novel diagnostic devices are paving the way for the noninvasive diagnosis of melanoma. One such device uses electrical impedance spectroscopy (EIS) to generate an EIS score that reflects the degree of cellular atypia in pigmented lesions (Nevisense, SciBase AB, Stockholm, Sweden). The device uses a handheld probe with a disposable electrode to measure the electrical impedance of a lesion. The pins on the end of the probe penetrate to the level of the stratum corneum to perform the procedure. This screening device is highly sensitive (97%) and has a specificity of 34% compared with histopathology.[28]

Ultrasonography

High-frequency ultrasonography can be used to evaluate the epidermal, subdermal, and subcutaneous tissues in real time.[29] However, this technology is both operator and equipment dependent for interpretation of results. It can be used to diagnose melanocytic skin lesions and subclinical metastatic foci near the lesion, which can facilitate the physician's decision to pursue further histopathologic analysis. Using the knowledge of lesion borders, volume, and depth can help clinicians minimize tissue loss and improve cosmetic outcomes.

Confocal microscopy

In vivo confocal microscopy can be a helpful adjunct to visual examination in diagnosing melanoma. In a study of 857 lesions, the addition of confocal scanning laser microscopy resulted in 96% and 97% correctly classified benign and malignant lesions, respectively,[30] compared with 80% benign and 85% malignant correctly classified lesions with visual examination alone.

GENOMICS IN MELANOMA DIAGNOSIS AND PROGNOSIS

Genomics in Decision to Biopsy

Clinically suspicious pigmented lesions have traditionally been sent for definitive diagnosis with biopsy. However, for patients with many suspicious nevi or nevi in cosmetically sensitive areas, biopsy is not always easily possible or accepted by patients.

A noninvasive genetic test has been developed that samples skin cells harvested by an adhesive patch for expression of 2 genes (Pigmented Lesion Assay, DermTech, La Jolla, CA)[31,32] (**Table 2**). The genetic material undergoes quantitative reverse transcriptase polymerase chain reaction (RT-PCR) and RNA expression levels of long intergenic non–protein-coding RNA 518 (LINC00518) and melanoma antigen preferentially expressed in tumors (PRAME) are determined. The test yields a low-risk, moderate-risk, or high-risk result for

Table 2
Genomic testing for melanoma

Clinical Query	Available Test
Diagnosis: decision to biopsy	2 GEP
Diagnosis: ambiguous lesions under light microscopy	23 GEP
Prognosis: risk of metastasis in 5 y ears	31 GEP

Abbreviation: GEP, gene expression profile.

each lesion. In line with other screening tests, this test has a high sensitivity of 91% and a specificity of 69% for melanoma.[31]

Genomics in Histopathologically Ambiguous Lesions

Melanomas can show a wide variety of histopathologic characteristics that may overlap with benign melanocytic lesions. In difficult cases, dermatopathologists now have the ability to order a 23 gene expression profile (GEP) test to differentiate benign from malignant melanocytic lesions (myPath Melanoma, Myriad Genetics, Salt Lake City, UT) (see **Table 2**).[33–35] The test analyzes the RNA expression of 23 genes within sample tissue. The test can be done with existing biopsy material and determines an outcome of benign, indeterminate, or malignant. The test has a sensitivity of 90% to 94% and a specificity of 91% to 96%. Studies have shown that this test increases definitive diagnoses and affects patient management decisions.[36,37]

Stage at Diagnosis

An analysis of 26,958 patients with melanoma in the Ohio Cancer Incidence Surveillance system found that black patients are 3 times more likely to present with stage 3 or 4 disease.[38] This rate may be caused by a lower index of suspicion for melanoma by these patients and physicians leading to a delay in diagnosis. Similarly, type of insurance significantly influenced the stage at diagnosis, with Medicaid patients twice as likely to present at higher stage than private insurance patients. This trend held for patients with Medicare and uninsured patients.

Reporting of Melanoma to Cancer Registries

All US states mandate reporting of melanoma to centralized cancer registries. However, physicians may not be aware of the reporting requirements or may choose not to comply with these mandates. A survey of 158 dermatologists found that only 34% of respondents routinely report newly diagnosed melanoma cases.[39] Less experienced practitioners and those who rarely encountered patients with melanoma in their practices were both less aware of reporting mandates and less likely to report cases if they were aware.

Surprisingly, when comparing the results of the 2017 study to a similar study conducted in 2010, respondents had lower rates of reporting to registries (44% in 2010 and 34% in 2017).[40] This widespread underreporting of melanoma may lead to significant underestimates of true incidence with resulting implications for resource allocation.

PROGNOSIS

Sentinel Lymph Node Status

Although tumor thickness is the most significant prognostic factor in melanoma, sentinel lymph node biopsy (SLNBx) status has been shown to be more significant in some models. However, the impact on survival of patients undergoing the procedure as well as its ability to alone fully predict survival remains controversial.

SLNBx has been associated with improved survival in some studies[41,42] and has been extensively criticized by other investigators.[43] A clinical trial of 1934 SLNBx-positive patients with melanoma randomized participants to completion lymph node dissection or nodal observation with ultrasonography.[44] The mean melanoma-specific survival rates at 3 years were similar in both groups. Although disease-free survival was slightly higher in the dissection group (68 months vs 63 months), patients in the dissection group developed lymphedema more often than those in the observation group. Therefore, completion dissection can control the regional disease but may not increase survival.

Genomics for Prognosis

A 31-GEP test has been developed for classifying patients with invasive melanoma into low risk and high risk for metastasis at 5 years (DecisionDx Melanoma, Castle Biosciences, Friendswood, TX) (see **Table 2**). This test uses RT-PCR to determine the differential expression of 31 genes (28 prognostic and 3 control genes) that vary in nonmetastatic and metastatic melanoma lesions. The test results (from low to high risk) are as follows: class 1a, class 1b, class 2a, and class 2b. The test does not require special processing of sample tissue and can be run on the primary biopsy specimen.

This test has been validated by multiple retrospective and prospective studies. The studies have consistently shown high sensitivity for recurrence, distant metastasis-free survival, and overall

survival.[45–47] One study of 256 patients who underwent 31-GEP testing found a negative predictive value of 99%, sensitivity of 77%, and specificity of 87%.[46] The 31-GEP test has also been shown to affect clinical management in the direction dictated by the test results (eg, higher-risk patients undergo more frequent follow-up, imaging, and laboratory testing).[48–50]

Adding the information obtained from the 31-GEP test to SLNBx status seems to significantly improve prognostic assessment.[51] Given that there are so many more SLNBx-negative patients, the absolute number of patients who die from melanomas that are SLNBx negative is greater than for those that are SLNBx positive. When used in SLNBx-negative patients, the 31-GEP test has been shown to identify most of those who subsequently develop distant metastatic disease.[51] Also, integrating the additional information provided by the 31-GEP test with the American Joint Committee on Cancer (AJCC) online prognostic model (www.melanomaprognosis.net) significantly improved prognostic assessment.[52]

For SLNBx-negative patients, the 31-GEP test identified more than 80% of those patients who went on to develop distant metastases and expire. For patients with thin melanomas, a higher-risk 31-GEP result was more significantly associated with recurrence-free survival than SLNBx status.[53]

MANAGEMENT

Time to Surgery from Biopsy

It is known that early detection and treatment of melanoma leads to better outcomes. An analysis of time from biopsy to excisional surgery in patients with melanoma found that stage I patients who undergo surgery more than 30 days after biopsy have increased mortality risk.[54] Thus, it is integral to patient safety that excisional surgeries be performed as soon as reasonably feasible after biopsy.

Sentinel Lymph Node Biopsy

The guidelines for performing SLNBx remain in flux. The 2018 National Comprehensive Cancer Network (NCCN) guidelines recommend routine SLNBx for patients with a greater than 10% positivity rate.[55] They do not recommend this procedure in patients with a less than 5% rate of positive biopsy. For patients between 5% and 10%, discussion of the risks and benefits of the procedure with patients is recommended.

The American Society of Clinical Oncology (ASCO) also released updated guidelines for the management and staging of melanoma in 2018.[56]

- Thin melanomas: ASCO does not recommend routine SLNBx for patients with nonulcerated lesions less than 0.8 mm in thickness (stage T1a). Biopsy can be considered for melanomas 0.8 to 1.0 mm or less than 0.8 mm with ulceration (stage T1b).
- Intermediate-thickness melanomas: ASCO recommends SLNBx for melanomas that are 1.0 to 4 mm thick (stage T2 or T3).
- Thick melanomas: ASCO states that SLNBx may be recommended for patients with melanomas greater than 4 mm thick after thoroughly discussing benefits and risks of procedure.
- Completion lymph node dissection: ASCO recommends that either completion lymph node dissection or observation can be offered to patients with low risk of micrometastatic disease. For higher-risk patients, observation can be offered after a thorough discussion of potential risks and benefits of completion dissection.

Among patients with melanoma who undergo SLNBx, 84% are negative, suggesting that these patients do not benefit from the procedure.[57] For elderly patients, in whom positive SLNBx is rare, the 31-GEP test has a negative predictive value for SLNBx status of 96%.[58,59] With a less than 5% chance of positive SLNBx in this population, the 31-GEP test could potentially reduce the need for this invasive procedure.

Targeted Systemic Treatments

Four classes of targeted systemic treatments have been developed to treat melanoma (**Table 3**). The

Table 3
Pathways for targeted therapies in melanoma

Targeted Antitumor Therapy		Immune Checkpoint Blockade	
BRAF	*MEK*	*CTLA-4*	*PD-1*
Vemurafenib	Trametinib	Ipilimumab	Nivolumab
Dabrafenib	Cobimetinib	—	Pembrolizumab
—	—	—	Atezolizumab

BRAF inhibitors interrupt the B-raf/MEK step of the activation pathway. However, these drugs only work on melanomas with the B-raf V600E mutation. MEK inhibitors target the mitogen-activated protein kinase enzymes, MEK1 and/or MEK2. Phosphodiesterase-1 (PD-1) blockers halt PD-1's negative regulation of T cell effector mechanisms, which increases the T cell's ability to elicit an immune response against cancer. CTLA-4 antibodies block CTLA-4's ability to inhibit T cell responses.

The newest approaches to the treatment of advanced melanoma include combination therapy, an established mainstay of oncologic treatment in other types of cancers. Many combinations using drugs for different targets are being studied. A combination of BRAF and MEK inhibition in patients with V600E mutations found significantly increased survival among patients with combination therapy compared with monotherapy.[60] Similar results have been found in patients treated with a combination of a PD-1 blocker and CTLA-4 antibodies.[61] Triple combination therapies of a PD-1 blocker, BRAF inhibitor, and MEK inhibitor have also been successful in decreasing tumor burden.[62]

Dermatologic Side Effects of Targeted Therapies

Patients on BRAF inhibitors are more likely to develop de novo melanomas, squamous cell carcinomas, and keratoacanthomas during treatment because of activation of the *ras* pathway leading to BRAF-negative, ras-positive, newly appearing tumors.[63] The risk for developing these new melanomas is increased more than 1700 times in these patients compared with the general population. This fact reinforces the importance of close follow-up examination for patients on these drugs.

Patients on nivolumab frequently develop serious adverse events (11%) such as pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis.[64] In another study, cutaneous adverse events were seen in 49% of patients.[65]

PATIENT FOLLOW-UP

Patients who have been diagnosed with melanoma in situ or invasive melanoma have a 15 times increased lifetime risk of developing a subsequent primary melanoma, which equates to a 20% lifetime risk for being diagnosed with a second melanoma. Therefore, patients with melanoma need to be followed closely not only for the spread of disease from their initial tumors but also for the development of additional primary melanomas. A survey of dermatologists found that, within 5 years of melanoma diagnosis, most dermatologists follow their patients every 6 months.[66] After 5 years, the most common follow-up interval for dermatologists increased to yearly visits.

Cure for Melanoma?

Although a cure for melanoma does not currently exist, the possibility is clearly on the horizon. Survival intervals for patients with metastatic disease are increasing with the use of targeted approaches. Longer-term follow-up data from patients treated in the phase I study with the PD-1 blocker nivolumab showed that, for the one-third of patients who survived for 3 years on this therapy, almost all continued to survive at 7 years.[67]

SUMMARY

Approaches to melanoma diagnosis, management, and therapy are rapidly changing. Noninvasive devices and genetic testing can be used to help diagnose melanoma before a biopsy is done. Genetic expression profiling can help diagnose ambiguous melanomas and better predict patient outcomes. The advent of targeted systemic therapies has evolved metastatic melanoma from an automatic death sentence into one in which a small percentage of patients now have extended survivals. Despite these advances, the incidence of melanoma continues to increase, which reinforces the importance of a comprehensive understanding of all aspects of this cancer by dermatologists and the need for continued research to help make a material impact on this cancer.

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